REMARKS

I. Status of the claims

Claims 1-25 are pending in the application and stand rejected. Claims 1-25 have been amended. New claims 26-29 have been added. No new matter has been added.

II. Claim Amendments

Claims 1-25 have been amended to delete the words "or ameliorating." Thus, the claims are directed to methods "of treating pulmonary infection" instead of methods of "treating or ameliorating pulmonary infection."

Claim 14 has been amended to recite subgenera of infections treated by the claimed method, while claim 26 has been added to recite certain species of the subgenera of claim 14.

Claim 1 has been amended to recite that the dosing is "from once a day to every week." Support for this amendment can be found in the claims as filed and in the specification at paragraph 24, which states that the dosing is preferably "once a day or less," and further states that in preferred embodiments, the dosing is "once every other day, once every third day, every week, or less." Moreover, specific examples of the claimed dosing are described in the specification at paragraph 68 and shown in Figure 7. The C.C.P.A. has found analogous limitations were adequately supported by the specification. *In re Wertheim*, 541. F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976); *see also* M.P.E.P. § 2163.05. In *Wertheim*, the specification described a range of 25% to 60 %, and specific examples of 36 % and 50% were also disclosed. A new limitation of "between 35% and 60%," however, was supported by the specification. Accordingly, Applicants submit that the specification as filed provides sufficient support for the limitation of "from once a day to every week." For the same reasons, the specification as filed supports new claim 27, which recites that

the dosing is "once a day, once every other day, once every third day, or every week." Claims 6-8, 11-13, 18-20 and 25 have all been amended to delete the words "or less." As explained above, the specification lists once a day, once every other day, once every third day, and once a week as preferred dosing. Accordingly, Applicants submit that the specification provides ample support for these amendments.

Claims 1 and 25 have been amended to recite that the liposomal/complexed antiinfective comprises at least one sterol, while new claim 28 specifies that the sterol is cholesterol. Support for this amendment can be found in the specification at paragraph 31, which states "[t]he sterol compounds are believed to affect the release and leakage characteristics of the formulation." Paragraph 30 of the specification specifically lists the sterols cholesterol and ergosterol. The examples further support this limitation. In paragraphs 60, 61 and 68, slow release of liposomal/complexed antiinfectives comprising cholesterol was demonstrated. (*See also* Figs. 3, 4 and 7 and *specification* at p. 20.) Applicants respectfully submit that the specification provides ample support for this amendment to claim 1 and new claim 28.

Claim 1 has also been amended to remove the term "cystic fibrosis," while new claim 29 specifies that the patient is a cystic fibrosis patient. Support for this amendment can be found in the specification at paragraph 7, which states "[a]lso provided is a method of treating or ameliorating pulmonary infection in an animal . . . ," thereby indicating that the claimed method can be used in any animal with a pulmonary infection. (*See also*, paragraphs 14, 18.) New claim 29 is supported by claim 1 as filed and the specification at paragraph 18. New claim 30 specifies that the infection is tuberculosis. Support for this amendment can be found in the specification at paragraph 18, which lists tuberculosis as an infection which can be treated using the claimed method.

Applicants respectfully submit that the amendments and new claims are amply supported by the specification, and no new matter has been added. Accordingly, Applicants request entry of these amendments.

III. Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-25 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states that the difference between the claim terms "treating" and "ameliorating" is not clear, and that these terms are redundant. (*Office Action* at p. 2.) Solely to expedite prosecution, Applicants have amended claims 1-25 to delete the term "ameliorating." Applicants submit that the scope of claims 1-25 has not been narrowed by this amendment.

The Examiner also contends that claim 14 is indefinite due to the claims terms listed in parentheses. (*Id.*) Applicants have amended claim 14 by rewriting the claimed subgenera of infections, *Pseudomonas*, staphylococcal, streptococcal, *Escherichia coli, Klebsiella, Enterobacter, Serratia, Haemophilus, Yersinia pestis, Burkholderia*, *Mycobacterium, M. fortuitum complex,* or *M. avium complex* in Markush format. New claim 26 has been added to further recite the claimed species of the subgenera of infections recited in claim 14. Support for this amendment can be found in claim 14 as originally filed, and in the specification at paragraph 18. For example, the specification states that "pseudomonas (e.g. *P. aeruginosa, P. paucimobilis, P. putida, P. fluorescens,* and *P. acidovorans*) . . ." can be treated with the methods of the present invention. Thus, the specification plainly indicates that *P. aeruginosa, P. paucimobilis, P. putida, P.*

fluorescens, and *P. acidovorans* are species of the infection subgenus pseudomonas. Accordingly, no new matter has been amended.

Applicants submit that the §112, second paragraph, rejections have been obviated by these amendments. Accordingly, withdrawal of this rejection is respectfully requested.

IV. Rejections Under 35 U.S.C. § 102(b) and 102(e)

The Examiner has rejected claims 1-25 as being allegedly unpatentable over U.S. Patent No. 5,662,929 to Lagace et al. ("Lagace"). To anticipate a claim under §102(b), a reference must teach each and every element of the claim, either expressly or inherently. M.P.E.P. § 2131. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union oil Co. of* California, 8144. F. 2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Furthermore, "[t]he identical invention must be shown in as complete detail as contained in the . . . claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1566 (Fed. Cir. 1990). Applicants submit that Lagace does not meet this standard.

Lagace describes liposomal formulations containing therapeutic agents, such as antibiotics. (*Lagace* abstract.) According to Lagace, "in order to maintain the desired characteristic of the liposome formulation, a low rigidity of the liposomes seems required." (*Id.* at col. 10, l. 67 to col. 11, l. 5.) Thus, Lagace avoids the use of cholesterol in the formulation. (*Id.*)

The present invention is directed to methods of "treating pulmonary infection in a patient comprising pulmonary administration of an effective amount of a liposomal/complexed antiinfective, wherein the (i) administered amount is 50% or less of the comparative free drug

amount, or (ii) the dosing is once a day, once every other day, once every third day, or every week, or (iii) both, and wherein the liposomal/complexed antiinfective comprises at least one sterol.

Lagace does not disclose liposomes comprising at least one sterol, as recited in amended claim 1. The liposomes of Lagace include DPPC, DMPG, and certain other phosphatidylcholines and phosphatidylglycerols. (*Lagace* at col. 8, ll. 41-47.) None of the lipids described in Lagace are sterols.

Additionally, Lagace does not teach dosing from once a day to every week, as recited in claim 1. The Examiner contends that the claim term once a day or less "includes even one dose. (*Office Action* at p. 3.) Applicants submit that the amendment of claim 1 to recite that the dosing is "once a day, once every other day, once every third day, or every week" obviates this rejection. Applicants submit that once at day, once every other day, etc. does not encompass a just a single, isolated dose. Moreover, Lagace describes experiments in rats, where the dosing occurred at 16 hour intervals. (*Lagace* at col. 12, ll. 16-18.)

The Examiner has also rejected claims 1-25 as being allegedly unpatentable under 35 U.S.C. § 102(e) over U.S. Publication No. 2005/0019926 to Gonda et al. ("Gonda"). The Examiner alleges that Gonda discloses lipid formulations containing amino glycosides for the treatment of bacterial disease in cystic fibrosis patients, and further, that the once a day or less encompasses even one dose. (*Office Action* at p. 3.) Applicants respectfully traverse.

To the contrary, Gonda describes compositions comprising nucleic acids complexed with a cationic aminoglycoside, where the nucleic acid is "condensed." (*Gonda* at ¶ 9.) The compositions of Gonda provide a "a means for introducing a nucleic acid and/or a gene product into a cell . . . ." (*Id.* at ¶ 10.) In certain embodiments of Gonda, the composition also includes one or more lipids or

polymers. (*Id.* at ¶ 57.) The "condensed" nucleic acid refers to the electrostatic interaction of the nucleic acid with polyvalent cationic species with a bout a 103 to 106 reduction in the volume of the nucleic acid. (*Id.* at ¶ 28.) Nucleic acids condensed with polyvalent cationic species are less susceptible to degradation by nucleases. (*Id.*)

Applicants submit that the nucleic acids complexed with cationic aminoglycosides to form a condensed nucleic acid species is not encompassed by the antiinfective of the present invention. Rather, the nucleic acid complexed with an amino glycoside is completely different chemical species, not encompassed by the instant claims. The definition of antiinfective provided in the instant specification is "agents that act against infections such as bacterial, mycobacterial, fungal, viral, or protozoal." (*Specification* at ¶ 15.) A variety of examples of such antiinfectives follows, including aminoglycosides. (*Id.* at ¶ 16.) Applicants submit that one of ordinary skill in the art would not consider a nucleic acid complexed with a cationic aminoglycoside, forming a different chemical entity for transfecting a cell with a gene, to be included in this definition.

Additionally, as explained above with respect to Lagace, Gonda does not disclose the recited dosing of once every day, once every other day, once every third day, or every week, and therefore, does not anticipate the instant claims.

For at least these reasons, Applicants respectfully request withdrawal of this rejection.

V. Rejections Under 35 U.S.C. § 103(a)

A. Gonda

Claims 1-25 stand rejected as being allegedly obvious over Gonda. The Examiner alleges that Gonda discloses liposomal formulations containing aminoglycosides for treating bacterial disease in cystic fibrosis patients. (*Office Action* at p. 4.) The Examiner admits that Gonda fails to

disclose the claimed dosing. (*Id.*) To remedy this deficiency, the Examiner contends that "whether the composition has to be administered daily or once a day and the dosage depend upon the severity of the condition, the age of the patient and other parameters," which are allegedly "obvious parameters manipulated by an artisan to obtain the best possible results. (*Id.*) Applicants respectfully traverse.

In order to establish a prima facie case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to the skilled artisan, to modify a reference or combine reference teachings. Second, there must be a reasonable expectation of success. The teaching or suggestion must be found in prior art or knowledge of one of ordinary skill in the art, not in the applicant's disclosure. Finally, the reference, or references when combined, much teach or suggest each and every claim limitation. M.P.E.P. 2143.

Applicants respectfully submit that the cited references do not teach or suggest each and every claim limitation.

As explained above, the nucleic acid complexed with a cationic aminoglycoside to form a condensed nucleic acid complexed with aminoglycoside is a different chemical species useful for transfecting cells with a gene. The skilled artisan would not be motivated by Gonda to provide a method of treating pulmonary infection using liposomal/complexed antiinfective, instead of the nucleic acid complexed cationic aminoglycoside. A proposed modification of a reference cannot render that reference unsatisfactory for its intended purpose. (M.P.E.P. § 2143.01.) The intended purpose of Gonda is transfection of cells with condensed nucleic acids. This purpose would fail in the absence of a nucleic acid condensed with the cationic aminoglycoside.

Additionally, the Examiner admits that Gonda fails to disclose the claimed dosing. Applicants submit that the present dosing is not merely an obvious parameter based on factors such as age of the patient. In present composition, the less frequent, e.g. once a day, and lower dosing can be achieved owing to the claimed liposomal formulation having at least one sterol, which provides a rigid liposome. The rigid liposome releases the antiinfective much more slowly than the free drug, thus providing higher antiinfective levels in the lung over a longer period of time. (*See Specification*, Figs. 2-7.) Thus, Applicants data presented in the figures and the examples demonstrates the non-obviousness of the presently claimed method.

For at least these reasons, Applicants submit that the present claims are not obvious over Gonda.

B. Beaulac

The Examiner also has rejected claims 1-25 over Journal of Drug Targeting, 1999, vol. 7, no. 1, pp. 33-41 by Beaulac et al. ("Beaulac") either alone or in combination with Gonda. According to the Examiner, Beaulac discloses a method of treating pulmonary infection by administering liposomal tobramycin. The Examiner admits that Beaulac fails to disclose the claimed dosing. (*Office Action* at pp. 4-5.) The Examiner relies on Gonda for teaching that the composition may used to treat cystic fibrosis patients. (*Id.*)

Beaulac discloses Fluidisomes™ - tobramycin compositions for treating *P. aeruginosa* infection in cystic fibrosis patients. According to Beaulac, rigid liposomes have low bactericidal activity in the mononuclear phagocytic system, owing to issues with uptake of rigid liposomes by phagocytes. (*Beaulac* at p. 34, col. 1.) Thus, Beaulac employs flexible liposomes, such as Fluidisomes, which contain DPPC and DMPG - non-rigid phospholipids.

Applicants submit that Beaulac teaches against the presently claimed method. Specifically, Beaulac *teaches against* a composition comprising an antiinfective and a liposome comprising at least one sterol, owing to Beaulac's expected low bactericidal activity in rigid liposomes. Thus, the skilled artisan, on reading Beaulac, would not use a sterol to form a rigid liposome in the presently claimed method.

Applicants further submit that the skilled artisan would not combine Beaulac and Gonda. As explained above, Gonda relates to transfection of cells with genes, while Beaulac is directed to Fluidisome-tobramycin compositions. Thus, the references are directed to completely different indications.

Additionally, the Examiner admits that Beaulac fails to disclose the claimed dosing. As explained above, Applicants submit that the present dosing is not merely an obvious parameter based on factors such as age of the patient. In present composition, the lower dosing can be achieved owing to the claimed liposomal formulation having at least one sterol, which provides a rigid liposome. The rigid liposome releases the antiinfective much more slowly than the free drug, thus providing higher antiinfective levels over non-rigid liposomes. Specifically, the Fluidisomes, which Beaulac specifically explains are not rigid, would not have the antiinfective release profile that makes the presently claimed dosing possible. Again, Applicants data presented in the figures and the examples demonstrates the non-obviousness of the present method. (*See Specification*, Figs. 2-7.)

For at least these reasons, Applicants respectfully request withdrawal of this rejection.

C. Lagace

The Examiner has rejected claims 1-25 as being obvious over Lagace. Applicants submit that Lagace fails to teach or suggest each and every limitation of the present claims. Specifically, Lagace fails to teach or suggest at least one sterol and the claimed dosing.

Like Beaulac, Lagace specifically teaches *against* the use of sterols to form the liposome. Instead, the liposomes of Lagace lack rigidity, thus precluding the claimed dosing schedule of once a day, once every two days, once every third day, or every week. Lagace emphasizes that "in order to maintain the desired characteristic of the liposome formulation, a low rigidity of the liposomes seems required. This low rigidity can be achieved by maintaining a low temperature of phase transition . . . and avoiding the use of cholesterol in the formulation." (*Lagace* at col. 10, l. 67 to col. 11, l. 5, emphasis added.) Thus, the skilled artisan would not use a sterol based on the teachings of Lagace.

As explained above, the claimed dosing is not merely an obvious parameter to be manipulated by the skilled artisan. The compositions used in the presently claimed methods, on the other hand, a sterol is required. Lower dosing can be achieved owing to the claimed liposomal formulation having at least one sterol, which provides a rigid liposome. The rigid liposome releases the antiinfective much more slowly than the free drug, thus providing higher antiinfective levels over non-rigid liposomes.

For at least these reasons, Applicants request withdrawal of this rejection.

D. Friesen

Finally, the Examiner has rejected claims 1-25 as allegedly obvious over U.S. Publication No. 2003/0118636 to Friesen et al. ("Friesen"). According to the Examiner, Friesen discloses lipid

vesicles for the delivery of drugs. The Examiner admits that Friesen lacks the claimed aminoglycosides and the claimed dosing. Applicants respectfully traverse this rejection.

Friesen describes lipid vesicles having proteinaceous channels, such as ion or mechanosensitive channels of large conductance (MscL) and small molecules, such that the small molecules is released via the proteinaceous channel. (*Friesen* at ¶ 7.) Thus, drug release occurs upon activation of the channel, and does not involve disruption of the lipid vesicle.

Applicants submit Friesen fails to teach or suggest each and every element of the claimed method. Specifically, Friesen fails to teach or suggest a liposomal/complexed antiinfective as claimed. Friesen discloses specific small molecules, none of which include the presently claimed antiinfectives. (*Friesen* at ¶ 83.) Nothing in Friesen teaches or suggests that the proteinaceous channels are suitable for use with the instant antiinfectives, such as aminoglycosides. Thus, the Examiner has provided no reasonable expectation for success in modifying the compositions of Friesen.

Furthermore, Nothing in Friesen teaches or suggests the claimed dosing. As explained above, the Applicants submit that the claimed dosing is a non-obvious feature of the presently claimed method owing to the specific liposomal/complexed antiinfective recited in the instant claims.

For at least these reasons, Applicants respectfully request withdrawal of this rejection.

VI. Double Patenting

Claims 1-25 stand rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 74-76, 78-84, 86-87, 94-95, 98-102 and 105-108 of copending Application Serial No. 10/383,173 ("the '173 application"), either alone or in

combination with Lagace. Applicants respectfully request that the Examiner hold in abeyance all obviousness-type double patenting rejections based on the '173 application until allowable subject matter is indicated.

VII. Conclusion

In light of the amendments and remarks set forth above, Applicants submit that the pending claims are in condition for allowance. Reconsideration and timely allowance of the pending claims is respectfully solicited. If a telephone conference would be helpful, the Examiner is invited to call the undersigned at 617-832-1223. Applicants hereby request that any additional fees required for timely consideration of this application be charged to **Deposit Account No. 06-1448, Reference TRA-008.01**

Dated: August 2, 2007

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